DETAILED ACTION

Status of the Application

The remarks and amendments filed on October 6th, 2010 are acknowledged. Claims 2-8, and 13-24 were canceled, claims 1, 9-12, and 16-16 are included in the prosecution.

Response to arguments

Withdrawn Objections/Rejections

Rejection of claims under 35 USC § 102 and 103

In view of applicant's cancellation of claims 2-8, and 12-14, and amendment of claims 1 and 9, the rejections of claims 1-3 and 10-12 under *35 USC § 102(b)* and claims 4-9 and 13-16 under *35 USC § 103(a)* are withdrawn.

Response to Applicant's Arguments Regarding Above Rejections

Though the same art used in the prior 102 and 103 rejections has been combined in a new 103 rejection, the new rejection was necessitated by applicant's significant amendment of claim 1. As such, applicant's arguments to the prior rejections are moot in light of the new grounds of rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 9-12, and 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and thereby its dependent claims, have the limitation of “grouping said human individuals who exhibit the same or similar characteristics”. There is no clear definition of what constitutes a “similar characteristic”. What is “similar”? There are no metes or bounds set forth in the claim to allow one to determine how one determines that certain individuals exemplify a characteristic, or how that characteristic defines a phenotype. As such the claim is rendered indefinite.

Claim 10 recites the limitation "at least one probe compound" in reference to claim 1, which has been amended to include more than one probe compound. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 is improperly dependent upon canceled claim 14, making it unclear as to which claim it depends from.

Claim 16 recites the limitation "at least one probe compound" in reference to claim 1, which has been amended to include more than one probe compound. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 9-12, and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Streetman, D.S., et al. (Pharmacogenetics, 2001) in view of Cook, et al., WO 2001/96895.

Streetman discloses a phenotyping method for determining the in vivo activity of the p450 CYP3A, which includes both isoforms CYP3A4 and CYP3A5, upon the probe compounds midozolam and fluvoxamine. Midozolam is a substrate for CYP3A and fluvoxamine is a CYP3A inhibitor. Meeting the limitation of determining in vivo CYP 450 activity for “more than one probe compound" as recited in instant claim 1. The specific CYP 450 isozyme CYP3A4 and substrate midozolam meet the limitations of instant claims 15 and 16. The procedure uses (LC/MS/MS) to study the biofluid urine. Meeting the limitation of instant claim 12.

Streetman teaches a method in which a group of several individuals are characterized for the ability to metabolize midazolam, these individuals are grouped, and this trial group was phenotyped multiple times, these individuals were compared to one another by thorough statistical analysis and the individuals were phenotyped 8 times. These teachings meet the limitations of steps c) and d) of instant claim 1. See page 350 paragraphs 6 and 7, page 351 paragraphs 1-3, and figure 2. The individuals were obviously phenotyped at least once before a second administration of the drug midazolam as claimed in instant claim 9.

Streetman does not teach the use of NMR, hyperpolarizing the nuclei of biofluid samples and probe compounds (such as by direct nuclear polarization (DNP)), analyzing samples by NMR spectroscopy, selecting the patients for use in a clinical trial, or using probe compounds enriched with NMR active nuclei.

Cook, et al. discloses a method for investigating the fate of a test compound by analyzing the compound and its metabolites using NMR. The procedure comprises the steps of hyperpolarizing, the enriched or non- enriched NMR active nuclei of a biological sample or biofluid containing one or more test compound(s), (such as by direct nuclear polarization (DNP)). See page 4 paragraphs 3 and 7, and claims 1-8. Cook states that mass spectrometry, such as that used by Streetman, is a useful technique for identifying metabolites, but that the use of hyperpolarized NMR is an improvement upon this technique. See page 2, lines 24-33, and page 3, lines 1-22. Cook also states that evaluating the fate of such test compounds can be used to evaluate patients and groups of patients in pre-clinical and clinical trial populations. See page 2, lines 5-21. Cook also states that the use of hyperpolarized NMR can allow for sensitive determination of drug metabolites which mass spectrometry may not be able to characterize on its own. See page 2, lines 25-30.

The method of Streetman, improved by the methods of Cook meet each and every limitation of the instant claims.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to improve the technique of Streetman using the hyperpolarized NMR technique taught by Cook in order to form a method for selecting patients for a

clinical trial. Cook expressly suggests the use of hyperpolarized NMR to improve metabolic drug studies carried out by mass spectrometry, such as the one taught by Streetman. As such, this combination is merely the application of a known technique to improve a similar method ready for improvement to yield predictable results.

The person of ordinary skill in the art would have been motivated to make these modifications, because of the express suggestion of Streetman to improve existing mass spectrometry identification methods, and reasonably would have expected success because both the methods of Streetman and Cook are complementary techniques, that are useful for identifying the metabolites found in patient's biofluids.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LANCE RIDER whose telephone number is (571)270-1337. The examiner can normally be reached on M-F 11-12 and 1-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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